ONCE DAILY FORMULATIONS OF TETRACYCLINES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation of U.S. application Ser. No. 12/155,676, filed Jun. 6, 2008, which is a Continuation of U.S. application Ser. No. 10/819,620, filed Apr. 7, 2004 now U.S. Pat. No. 7,749,532, which claims priority to U.S. Provisional Application Ser. Nos. 60/460,963, filed Apr. 7, 2003, and 60/547,964, filed Feb. 26, 2004.

FIELD OF THE INVENTION

The present invention is concerned with once-daily compositions of tetracyclines, which can be used for the treatment of acute or chronic diseases, for instance those with inflammatory components. More specifically, the present invention is directed to a pharmaceutical composition of doxycycline for the treatment of diseases or conditions in which collagen destructive enzymes or molecules involved with such things as inflammation are contributing factors, and which is a once daily formulation. The compositions are especially useful for treating such common disease states as periodontal disease, rosacea, dry eye, acne and rheumatoid arthritis.

BACKGROUND OF THE INVENTION

Conventionally, doxycycline and related tetracyclines are used as broad spectrum antibiotics to treat various bacterial infections. Tetracyclines interfere with the protein synthesis of Gram positive and Gram-negative bacteria by preventing the binding of aminoacyl-tRNA to the ribosome. Their action is bacteriostatic (preventing growth of bacteria) rather than killing (bactericidal). The doses commonly used for doxycycline to achieve the antibiotic effect are 100 mg and 50 mg.

Doxycycline, as well as other tetracyclines, also has other therapeutic uses in addition to its antibiotic properties. For example, doxycycline is known to inhibit the activity of collagen destruction enzymes such as collagenase, gelatinase, and elastase. Its collagenase inhibition activity has been used to treat periodontal disease. For another example, doxycycline can inhibit lipase produced by the bacterium *P. acnes* and thus reduces the availability of free fatty acids that are involved in inflammation. Doxycycline may also reduce inflammation by reducing cytokine levels so that the integrity of the follicular wall is preserved. Thus, doxycycline also has the potential in treating skin diseases, such as acne.

Investigators have found that sub-antimicrobial doses of tetracyclines are useful in the treatment of various ailments, although the mechanisms responsible for the effects are not entirely clear. For instance, U.S. Pat. No. 6,455,583 discloses treating meibomian gland disease by oral administration of non-antimicrobial amounts of a tetracycline to the patient. U.S. Pat. No. 6,100,248 teaches a method of inhibiting cancer growth by administering tetracyclines which have been chemically modified to attenuate or delete their antibacterial activity. Methods to reduce collagenolytic enzymes by administration of amounts of a tetracycline that are generally lower than the normal amounts used for antimicrobial therapy are disclosed in U.S. Pat. No. 4,666,897. The patents cited in this paragraph are hereby incorporated herein by reference.

In the market, there are two implantable products for site-specific use in the treatment of periodontal disease. The PerioChip® is a small, orange-brown chip, which is inserted into periodontal pockets. Each PerioChip® contains 2.5 mg of chlorhexidine gluconate in a biodegradable, resorbable matrix. It is recommended that PerioChip® treatment be administered once every three months in pockets that remain at 5 mm or deeper. A second product, Atridox®, is an injectable, resorbable gel, which provides the subgingival controlled-release of 42.5 mg doxycycline for approximately one week. Additionally, there is now available a new oral medication called Periostat®, which delivers 20 mg doxycycline systemically as a collagenase inhibitor used in patients with adult periodontal disease. Most people would prefer to take a pill to the implant. However, Periostat® requires twice daily dosing and raises concerns about patient compliance. Thus, it would be highly beneficial to develop a once-a-day formulation for doxycycline.

While doxycycline is generally effective for treating infection, the use of doxycycline can lead to undesirable side effects. For example, the long-term administration of the antibiotic doxycycline can reduce or eliminate healthy biotic flora, such as intestinal flora, and can lead to the production of antibiotic resistance organisms or the overgrowth of yeast and fungi. Because of the undesirable side effects from its antibiotic properties, there is a need for a unique dose and an improved formulation to deliver doxycycline such that the anti-collagen destructive enzymes or other such beneficial effect of tetracyclines, especially doxycycline, is attained, but antibacterial effects are avoided.

SUMMARY OF THE INVENTION

The present invention is in its broadest sense directed to pharmaceutical compositions of tetracyclines designed to provide an extended release profile in vivo of levels of active ingredient that at steady state are high enough to be effective to have a beneficial effect in the treatment of a disease or condition, but not as high as to exert an antibacterial effect. Such pharmaceutical compositions are formulated into dosage forms that can be taken once a day.

One object of the present invention is to provide a pharmaceutical composition of doxycycline, which can be given once a day yet meet the steady state blood levels required for the treatment or prevention of diseases or conditions caused by overproduction of collagenase, such as periodontal disease, or other biochemicals associated with certain disease states which could be regulated with doxycycline, such as conditions involving inflammation, without the undesirable effects of long term antibiotic activity.

One object of the present invention is to provide a once-daily pharmaceutical composition containing doxycycline that will give steady state blood levels of doxycycline of a minimum of about 0.1 μg/ml and a maximum of about 1.0 μg/ml.

In one aspect of the invention is an immediate release formulation of doxycycline containing less than 50 mg but more than 25 mg, preferably about 40 mg. doxycycline base.

In another aspect, the invention is directed to a pharmaceutical composition of doxycycline that contains an immediate release (IR) component of the drug and a delayed release (DR) component of the drug, which are combined into one dosage unit for once-daily dosing. The components can be present in various ratios, although preferred are ratios of about 70:30 to about 80:20, and most preferred 75:25, IR:DR, with the total dosage of doxycycline being less than about 50 mg. and preferably about 40 mg. The ratio refers to the dose breakdown between IR and DR, e.g., 80:20 means 80% of 40 mg is from IR portion and 20% of 40 mg is from DR portion.

Yet another object of the invention is to provide a method for treating diseases or conditions in which collagenase is